



# Combining Raman Spectroscopy and Differential Scanning Calorimetry

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## Introduction

Raman spectroscopy is a powerful technique for materials characterization in its own right, having found applications in as diverse areas as polymorph identification in pharmaceuticals, crystallinity studies in polymers, and reaction monitoring to name a few. Recently the use of Raman spectroscopy with a hot stage has become common and the applications of the technique keep expanding.

Why combine Raman spectroscopy with Differential Scanning Calorimetry (DSC) then? DSC adds several capabilities to a combined instrument.

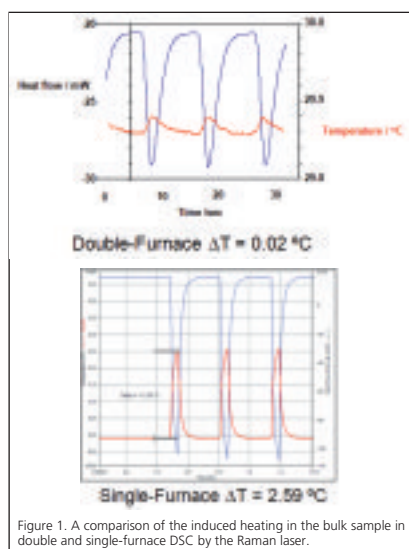


Figure 1. A comparison of the induced heating in the bulk sample in double and single-furnace DSC by the Raman laser.

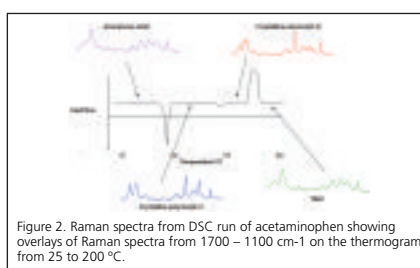


Figure 2. Raman spectra from DSC run of acetaminophen showing overlays of Raman spectra from 1700 – 1100 cm<sup>-1</sup> on the thermogram from 25 to 200 °C.

DSC is a commonly used technique in many of the same industries as is Raman Spectroscopy. DSC requires extremely good temperature control and easily exceeds the control found on hot stages. Temperatures are extremely stable and, in double-furnace designs, isothermal performance is excellent. Since variation of a few degrees can change the form of many materials, this control and precision is important. DSC offers other advantages: the major use of DSC is to determine the precise temperature of a transition and the energy of that transition. Transition temperatures are used as indicators of changes in physicochemical properties of most polymeric and pharmaceutical materials. Measuring subtle shifts in these temperatures is important in tracking these properties. More importantly the energy of these transitions is very important in understanding material properties. For example, in a polymeric material the energy of the melting peak gives you

the enthalpy of melting, which is a function of the crystallinity of the material. In pharmaceuticals, the enthalpy tells you about the type of polymorphic rearrangement you have and can be useful in determining pseudo-polymorphism.

Combining the two techniques allows one to strengthen the interpretation of the data over each technique alone. For example, Raman spectroscopy will see the conversion of one polymorphic form to another while the DSC gives you the energy needed for that transition and the precise temperature at which it occurs. In addition, as double furnace DSC controls temperature directly, it will prevent the Raman laser from causing bulk heating in the sample. As we will see, this is a significant concern.

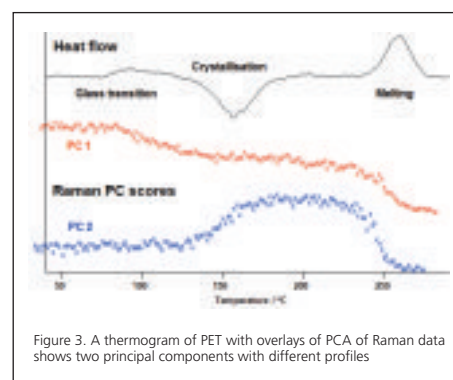


Figure 3. A thermogram of PET with overlays of PCA of Raman data shows two principal components with different profiles

## Considerations in Making DSC-Raman Spectroscopy Work

Combining the two techniques allows one to apply the precise temperature control of the DSC with the ability of Raman to detect the different polymorphic structures allowing precise characterization of the material. As an example, consider the common painkiller, acetaminophen. Raman spectroscopy has identified the three solid state forms of this material found under these experimental conditions. (There is a fourth form not seen here.) Combining this technique with DSC allows us to measure precisely the temperatures at which they occur. Figure 2 shows the DSC run on a sample of acetaminophen. The thermogram shows 2 exothermic events believed to correspond to polymorphic changes in the material as well as

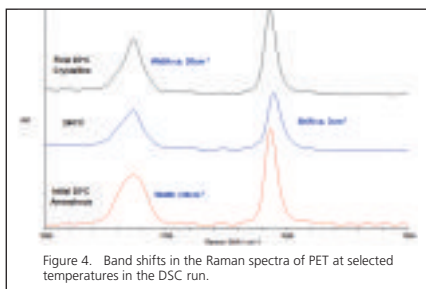


Figure 4. Band shifts in the Raman spectra of PET at selected temperatures in the DSC run.

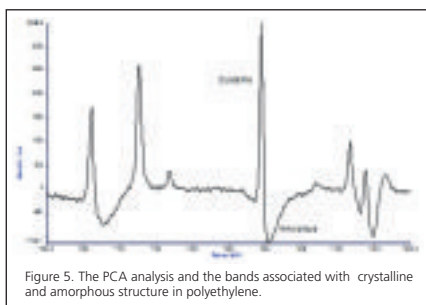


Figure 5. The PCA analysis and the bands associated with crystalline and amorphous structure in polyethylene.

the endothermic melt. When DSC-Raman is done, the Raman spectra show the conversion to Form II at  $\sim 90^\circ\text{C}$  and then to Form III at  $\sim 151^\circ\text{C}$  before melting. This greatly simplifies the understanding of the thermal behavior of the material and is much more conclusive than attempting to draw this information out of either conventional and/or modulated temperature DSC or Raman spectroscopy alone.

One, the ideal sample geometries are quite different and this leads to several problems. The DSC sample is placed in a metal pan that is several millimeters in diameter and is best presented as a thin layer on the base of the pan for optimum heat transfer, which results in weak Raman intensities when short collection times are necessary. Additionally, the quartz windows used to contain the sample will reduce the signal. Finally the small area (typically  $100\mu\text{m}$ ) from which the Raman signal is collected raises the question of whether the measurement is representative. DSC sample pans are often sealed both to maintain a good sample environment and to protect the instrument from off gassing but to obtain Raman spectra the pan has to be open or covered by a quartz window. Both of these choices can adversely affect the DSC performance.

A second issue, the energy from the

laser must be dissipated, thus will also affect the heat flow as well as causing localised heating that may distort the DSC data. In extreme cases the laser heating may induce transitions before they occur in the rest of the sample. These problems are much worse in single-furnace, heat flux DSC than in double-furnace, power controlled DSC. Figure 1 shows the affects of the laser induced heat gain in the bulk sample. Use of a double furnace DSC greatly decreases these effects. The presences of spikes in the heat flow data caused by the laser still must be dealt with by a software method, but this is relatively easy.

Finally, the introduction of the probe into the DSC environment creates a path for heat loss from the specimen, and in the case of sub-ambient operation, a path for moisture to get in and cause frosting. These can be addressed by proper design of the coupling system and proper choice of the purge gases used. In many cases, where sub-ambient application isn't needed, no problem is found. Heat loss at high operating temperatures is not really an issue as the black body radiation swamps the Raman spectra at temperatures higher than  $350\text{-}400^\circ\text{C}$ .

## Applications of DSC-Raman Spectroscopy

Combining the two techniques allows one to apply the precise temperature control of the DSC with the ability of Raman to detect the different polymorphic structures allowing precise characterization of the material. As an example, consider the common painkiller, acetaminophen. Raman spectroscopy has identified the three solid state forms of this material under these experimental conditions. (There is a fourth form not seen here.) Combining this technique with DSC allows us to measure precisely the temperatures at which they occur. Figure 2 shows the DSC run on a sample of acetaminophen. The thermogram shows 2 exothermic events believed to correspond to polymorphic changes in the material as well as the endothermic melt. When DSC-Raman is done, the Raman spectra show the conversion to Form II

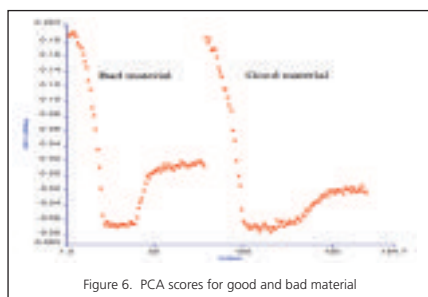


Figure 6. PCA scores for good and bad material

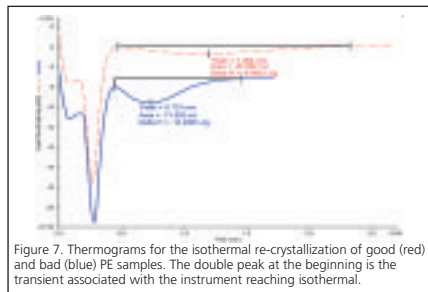


Figure 7. Thermograms for the isothermal re-crystallization of good (red) and bad (blue) PE samples. The double peak at the beginning is the transient associated with the instrument reaching isothermal.

at  $\sim 90^\circ\text{C}$  and then to Form III at  $\sim 151^\circ\text{C}$  before melting. This greatly simplifies the understanding of the thermal behavior of the material and is much more conclusive than attempting to draw this information out of either conventional and/or modulated temperature DSC or Raman spectroscopy alone.

While the transitions here are exothermic, other polymorphic materials show changes caused by the loss of water or some other solvate from the molecule that appear as endothermic transitions. While Raman spectroscopy with a hot stage might determine the changes in the material accurately, without the understanding of the thermal data and the energy of transition, it is possibly for a water loss to be seen as a polymorphic rearrange. In DSC, we could detect this is an endothermic event and hence suspect. Other DSC methods can then be used to clarify the issue.

In applying DSC-Raman spectroscopy to polymers, the ability to understand crystallinity is an obvious area. Semi-crystalline and crystalline polymers are of great economic importance and understanding their behaviour is of great concern. For example, PET (polyethylene terephthalate) that has been rapidly cooled from the melt has a considerable amorphous content, which makes it clear. On heating it undergoes a glass transition and crystallisation. This example was cooled in the DSC at  $200^\circ\text{C}/\text{minute}$ . The glass transition is clearly visible in the heat flow curve but is not seen in the Raman data (Figure 3). The spectral changes are relatively small consisting of band broadening and small band shifts. The curve derived from PCA does show the crystallisation and melting events, but is very noisy.

The major change associated with these is broadening of the  $1726\text{cm}^{-1}$  C=O band. There are also band shifts that vary almost linearly with temperature (Figure 4). The DSC data clarifies the situation by clearly showing the strong endothermic peak that corresponds to crystal formation on heating. Here we see the reason the material is so much more crystalline before the melt than at the start of the run is the large amount of it that crystallizes during the run.

DSC-Raman can also be done using both controlled cooling and isothermal re-crystallization experiments. These approaches as well as fast scan DSC and modulated temperature DSC allow us to change the way the sample is heated and cooled to manipulate its properties and to trap or exclude certain transitions. In the case study here, two PE samples, a good and a bad, were first fast heated to above their melting temperature and then cooled slowly to room temperature. All the data from each of the runs of the 2 samples was put into PCA models. The data were normalized to allow for differences between the samples. There is a single important PC which shows narrow bands from the crystalline phase and broad bands from the amorphous. (Figure 5) The scores for the two samples show crystallization for both samples. For the controlled cooling, the scores plots for heating and cooling of the two samples are very similar. The top two pictures are direct from the PCA program. The noise levels in the plots are too high for any major differences to be seen but the general shape of the curves suggests the bad material is faster at crystallizing (Figure 6). The associated DSC runs show that the material gives a nice distinct crystallization peak on cooling and small differences are noted here that



were not as apparent in the Raman spectra. These are very small however and a more aggressive type of cooling was then used to enhance these differences.

For the isothermal studies, the samples were heated to above the melt as before, but then cooled at 200 °C/min to a temperature where polyethylene was known to re-crystallize. The Raman Spectrometer can collect data during the rapid heating of the material to the melt – although the fast heating will limit the number of spectra collected - and then on both the cooling and isothermal hold stages. After this experiment, the data is more conclusive in the Raman as well as in the DSC. The scores for the two samples show crystallization for both samples. For the starting materials and the high temperature form the scores are similar for both samples (Figure 7). After the re-crystallization, it appears that the degree of crystallization is greater for the 'bad' sample than for the 'good'. The final spectra clearly show that the 'bad' sample ends up more crystalline. The sharp bands are stronger relative to the broad bands from the amorphous material. Taking the melt as a starting point, we obtain a value of about 50% more amorphous in the good, confirmed by subtraction of the melt spectrum from the final spectra of each.

There is an isolated band from crystalline material at  $1125\text{cm}^{-1}$  that can be used to normalize between the two samples. The normalization limits quantitative interpretation but on a relative scale it appears that the final crystalline content of the 'bad' sample is about 30% higher than that of the good one.

In addition, the material responds re-crystallizes faster as seen in Figure 7. Looking at the enthalpy of crystallization, we find the bad material has a higher value of  $-71.00$  mj/gram while the good is much lower at  $-44.96$  mj/g. This gives us roughly a 35% difference in crystallinity between the two materials. Interesting, neither sample comes close to the crystallinity of the material at the start. Some of this is probably due to orientation in the material, but a large part is due to higher cooling rates used in making the films that were used here.

Together the DSC and Raman data explain the problems with the bad sample are due to the material responding differently to cooling and becoming more crystalline.

## Conclusions

DSC-Raman spectroscopy is a powerful tool for gaining greater understanding of material behavior, whether it is a polymer or pharmaceutical. Combining Raman spectroscopy's ability to elucidate chemical and structural information with DSC's precise measurement of temperatures and the energy of events allows us to gain a fuller picture of how a material behaves.



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